

Therapeutic procedure in small cell lung cancer

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ABSTRACT

Small cell lung cancer (SCLC) represents 12.95% of all lung cancer diagnoses and continues to be a major clinical problem, with an aggressive clinical course and short disease-free duration after 1st line therapy. Treatment of SCLC remains challenging because of its rapid growth and development of drug resistance during the course of the disease. Chemotherapy remains the current optimal treatment and radical thoracic radiotherapy representing the best treatment option for fit patients with LD. Platinum-based chemotherapy is the treatment of choice in patients with good performance status, and the effect of cisplatin is important for concurrent chemoradiotherapy in LD cause of his radiosensitivity. Patients with progress disease after first-line chemotherapy have poor prognosis. Second-line therapy may produce a modest clinical benefit. A number of targeted agents have been investigated in LD and ED, mostly in unselected populations, with disappointing results. Prophylactic cranial irradiation (PCI) is recommended only for patients who had full response to first line chemotherapy, as target of improving overall survival and decreasing possibilities of brain metastases. New factors for target therapy are the hope for the management of this systematic disease. If we identify these targets for treatment of SCLC and overcome drug-resistance mechanisms, we will create new chemo-radiotherapy schedules for future.

KEY WORDS

Small cell lung cancer (SCLC); treatment; chemotherapy; targeted

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Introduction

Lung cancer is one of the first cause of cancer death in the USA (1). First time described and identified in 1959, as a lung cancer with clinical and overall survival prognosis significantly different from non-small cell lung cancer (NSCLC), who was more common till this year. The proportion of small cell lung cancer (SCLC; among all lung cancer histological types) decreased from 17.26% in 1986

to 12.95% in 2002 (2). The proportion of women with SCLC increased from 28% in 1973 to 50% in 2002 (3). Further results after then are poor First line chemotherapy based in cisplatin and remain the only treatment for extensive SCLC who increase overall survival with the same toxicity (4). SCLC has high rate of initial response to chemotherapy (60-70%) in patients with extensive disease but mean survival is not better than 10 months because 70% of patients with SCLC are diagnosed with advanced disease with aggressive clinical course. This review focuses on the therapeutic procedure and management of SCLC.

Search method

Our search strategy for the selection of articles is described below. We searched the Medline databases for articles published between January of 1996 and October of 2013. In addition, we searched The Physician Data Query database for clinical

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trials and the proceedings of the American Society of Clinical Oncology, the American Society for Therapeutic Radiology and Oncology [1992-2013], the European Society of Therapeutic Radiology and Oncology [2000-2013], and the European Society for Medical Oncology [1998-2013] for relevant abstracts. Relevant articles and abstracts were selected and reviewed and the corresponding lists of references were scanned for additional studies.

Staging system

We have two systems to stage SCLC: (I) The tumour-node-metastases (TNM) classification (5), that used for NSCLC; and (II) The VA Lung Study Group (VALSG) limited disease-extensive stage (LD-ED) system. The Veterans' Administration Lung Study Group (VALSG) two-stage classification scheme has been routinely used for the clinical staging of SCLC since the late 1950s (6). The VALSG system defines limited-stage (LS) as: (I) disease confined to one hemithorax, although local extension may be present; (II) no extrathoracic metastases except for ipsilateral supraclavicular lymph nodes if they can be included in the same radiation port as the primary tumor; and (III) primary tumor and regional nodes that can be adequately encompassed in a radiation port. Extensive-stage (ES) disease is defined as disease that cannot be classified as limited, including malignant pleural or pericardial effusions, contralateral hilar or supraclavicular lymph nodes, and hematogenous metastases. In 1989 (7), the International Association for the Study of Lung Cancer (IASLC) proposed a modification of the VALSG system in which LS-SCLC was expanded to include contralateral mediastinal or supraclavicular lymph node metastases and ipsilateral pleural effusions independent of cytology (8). ES-SCLC remained any disease at sites beyond the definition of limited disease. Although the IASLC system has a higher discriminatory power (9), the VALSG system continues to be widely utilized, probably because of its simplicity. Recently, the IASLC has proposed that the newly revised TNM staging classification for lung cancer [American Joint Committee on Cancer (AJCC) 7th edition] (10) should replace the VALSG system for the staging of SCLC. This recommendation is based on a prognostic analysis of 8,088 patients with SCLC in the IASLC database with adequate data to determine clinical (c) or pathologic (p) TNM stage (11,12). Many trials for LD exclude patients with isolated pleural effusions (13-15), but overall survival of patients with pleural effusions is approximately same to other patients with LD-SCLC (16,17). Supraclavicular lymph node metastatic disease, may predict for inferior survival (18,19).

Therapeutic management

The gold standard first line chemotherapy as treatment of

limited-stage SCLC is cisplatin plus etoposide in parallel with thoracic radiation therapy, but treatment of extensive-stage disease is only chemotherapy with cisplatin plus etoposide. Surgical resection reserved for patients with small, node-negative disease staged as a very limited disease. Prophylactic cranial irradiation (PCI) reduces possibilities of brain metastases and prolongs overall survival in patients who have responded to chemotherapy.

Chemotherapy

1st line chemotherapy

SCLC is more chemosensitive (20) than all other types of lung cancer. First trials in the 1970s tried effectiveness of cyclophosphamide, doxorubicin/epirubicin and vincristine [CA(E)V] in SCLC (21-23). But after introduction of etoposide, comparing etoposide-cisplatin (EP) with CA(E)V found EP inferiority with better results about disease free and overall survival in patients with limited stage disease. The response rates were higher with EP in patients with ED, but without a survival benefit (24,25). After then, EP is better tolerated as the regimen of choice for initial treatment of SCLC (26).

Carboplatin in many trials is used instead of cisplatin in combination with etoposide (27) without differences in response rates, but significantly less toxicity (28). In clinical practice, with carboplatin reduce the risk of emesis, neuropathy, and nephropathy. The use of carboplatin has a greater risk of myelosuppression than the use of cisplatin. Additioning paclitaxel with cisplatin or carboplatin plus etoposide promised similar results in phase II trials but did not improve survival, and has association with unacceptable toxicity in a phase III study (29). Using maintenance or consolidation chemotherapy 4 to 6 cycles of standard treatment created a minor prolongation of duration of response but without improving overall survival and with greater risk of toxicity (30,31). The combination of irinotecan and a platinum agent has provided the greatest challenge to EP. A phase III trial performed in Japan found that patients with extensive-stage SCLC who were treated with irinotecan plus cisplatin had a median survival of 12.8 months, greater than 9.4 months for patients who treated only with EP (32). Till now, the community continues to recommend etoposide plus platinum as the standard regimen for patients with SCLC.

2nd line chemotherapy

At present, topotecan is the only drug approved by the US Food and Drug Administration for relapsed SCLC, and is considered the standard second-line chemotherapy in many countries. More recently, amrubicin has also shown more favorable antitumor activity, and is the most promising at present.

Topotecan is proposed as monotherapy for patients with relapsed SCLC with SD or PD after first line chemo-radiotherapy.

Table 1. Future targeted treatment.

Pathway	Treatment
Hedgehog	Vismodegib
VEGF	Aflibercept
IGF-1	Linsitinib, Cixutumumab
PI3K/Akt/mTOR	Temsirolimus
Aurora A kinase	Alisertib
Immune modulator	Ipilimumab

IGF-1, Insulin like growth factor-1; VEGF, Vascular endothelial growth factor; PI3K, Phosphatidyl inositol 3 kinase; Mtor, mammalian target of rapamycin.

For Topotecan the first positive opinion came from the "Committee for Human Medicinal Products (CHMP) on 24 January 2008" as monotherapy for the treatment of adult patients with relapsed SCLC for whom re-treatment with the first line regimen is not considered appropriate (30). Data from phase II studies suggested that amrubicin, an anthracycline, promised activity in patients with relapsed or refractory SCLC with the most common problem of grade 3/4 toxicity, primarily neutropenia (33,34). A randomized phase II trial suggested that amrubicin could be more effective than topotecan as second-line therapy in patients with relapsed SCLC, with response rates of 44% and 15%, respectively ($P=0.02$) (35,36).

Thoracic radiation

Most of patients with LD-SCLC treated only with chemotherapy. However, thoracic radiation therapy (TRT) can provide local control. In the other side cannot improve results on overall survival disease control (37). Many randomized trials tried to combine them to achieve better overall disease control. Although chemotherapy achieves high response rates, its use alone is associated with fairly high intrathoracic recurrence rates. Thoracic irradiation at doses not inferior to 40 Gy can induce local response, but by itself is unable to achieve good disease control. Combination therapy, consisting of thoracic irradiation and chemotherapy, produced better survival than chemotherapy alone in some trials (38,39) although other trials using cyclophosphamide-based therapy failed to show a survival benefit when irradiation was added (40).

The National Cancer Institute of Canada found that patients who received more than 37.5 Gy (Gray) had a better local control than those who received less than 25 Gy (40), but without better results in overall survival. An analysis of patients in three different dose chemoradiation trials, who treated with 45, 55 and 65 Gy found similarity in local control of disease and overall survival with the three doses analyzed. Suggested a dose at least 45 Gy for adequation local control (41).

The most commonly utilized fractionation schedules suggest single daily treatments of 1.8 to 2.0 Gy, five times per week, over 5 to 6 wks. Hyperfractionated radiotherapy found that improves local control and survival by using higher doses of radiation given in a shorter time. A randomized phase III trial (41), showed that patients who received the accelerated twice-daily schedule had better median survival (23 vs. 19 months), and 5-year overall survival (26% vs. 16%). A meta-analysis (41) suggested that there was no difference between early or late TRT on overall survival and there was a significantly improved 5-year overall survival with early TRT.

PCI

Brain metastasis is very common in patients with SCLC. Approximately 25 percent of patients have brain metastases at the first diagnostic procedure (42). A lot of trials evaluate the role of PCI in SCLC (43,44) with variation in their findings. PCI is recommended for patients with extensive-stage disease with a complete or partial response (45,46). The recommended regimens for PCI include not less than 24 Gy per day (46). Higher doses (e.g., 36 Gy) increased mortality and toxicity when compared with standard doses (25 Gy) (47). PCI should not be given concurrently with systemic chemotherapy, and high total radiotherapy dose (>30 Gy) should be avoided because of the increased risk of neurotoxicity. Fatigue, headache, and nausea/vomiting are the most common acute toxic effects after PCI (48).

Surgery

SCLC is considered as a systemic disease, and the role of surgery in the management of these patients (49-51) not exist in clinical practice. However, recent studies showed better results for surgical resection but only in early stage disease (very limited disease) (52). In contrast, there is currently no role for resection in the multimodality treatment of locally advanced SCLC.

Palliative treatment

Radiotherapy can provide excellent palliation for patients with localized symptomatic sites of disease (e.g., painful bony lesions, spinal cord compression, and obstructive atelectasis) or with brain metastases (53-55). Orthopedic stabilization may be useful in patients at high risk for fracture because of osseous structural impairment.

Future

Targeted biological therapies for SCLC are now being investigated, and although a great deal of research remains to be done, these agents may provide the hope for future treatment of SCLC (Table 1).

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